

HYDRAZINE DERIVATIVES OF THE CARBONIC AND THIOCARBONIC ACIDS

BY

PERRY ROSS KIPPUR

B.S., University of Denver, 1949

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AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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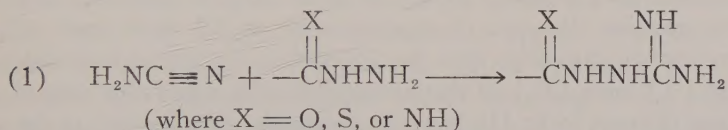
The author is sincerely appreciative of the patience, encouragement and assistance of his wife, Annette, during the course of his college training.

HYDRAZINE DERIVATIVES OF THE CARBONIC AND THIOCARBONIC ACIDS

INTRODUCTION

The potential use of hydrazine as a specialty fuel and the commercial exploitation of certain hydrazine derivatives as a result of their biological activity has recently increased the amount of research activity in this field. These efforts have been directed towards the development of new procedures for both the preparation of hydrazine and the synthesis of hydrazine derivatives that may be employed as pharmaceuticals and agricultural chemicals.

The purpose of this investigation has been first, to develop a practical method for the preparation of thiocarbohydrazide, a compound which exhibits insecticidal, herbicidal, fungistatic and growth regulating properties and secondly, to condense cyanamide with certain hydrazides in order to extend further the general type reaction involving the addition of hydrazine, N-substituted hydrazines and hydrazides across the triple bond of the cyano group.



I. THIOCARBOHYDRAZIDE

HISTORICAL

Thiocarbohydrazide has been prepared by the elimination of hydrogen sulfide from hydrazinium dithiocarbazinate (1) and the hydrazinolysis of S-methyldithiocarbazinate (2), diethyl xanthate (3) and thiophosgene (1) (4).

The amphoteric character of thiocarbohydrazide is evidenced by its solubility in acids and bases and the formation of metallic and acid salts in suitable solvents. Thiocarbohydrazide enters into the reactions typical of the hydrazide group 1) reduction of silver ion, 2) solvation of compounds containing the cyano group (HOCN, HSCN) to produce normal or substituted N-carbamyl or N-thiocarbamyl derivatives, 3) solvolysis of acyl halides to yield N-acyl derivatives and 4) solvolysis of carbonyl compounds to yield the corresponding thiocarbohydrazones. Although alkylation of thiocarbo-

hydrazide results in the formation of S-substituted derivatives, N-alkyl and N-aryl derivatives may be prepared by the reaction of certain thio compounds (CS_2 , CSCl_2) with substituted hydrazines. The 1,5-di-alkyl and/or aryl thiocarbohydrazides may be oxidized to "thiocarbazoness" ($\text{RN} = \text{NC}(\text{S})\text{NHNHR}$) which are useful in the quantitative, colorimetric determination of metallic ions.

EXPERIMENTAL AND DISCUSSION

The solubility of thiocarbohydrazide in water, ethanol, chloroform, carbon tetrachloride and hydrazine hydrate has been measured quantitatively; appreciable solubility is found only in the case of hydrazine hydrate. Thiocarbohydrazide is non-hygrosopic up to and including a relative humidity of 90%. It undergoes gradual thermal decomposition at 110°C . The pH of a saturated solution at room temperature is 6.95. From an x-ray diffraction pattern of thiocarbohydrazide, the d-spacings have been calculated.

A practical method for the preparation of thiocarbohydrazide by the direct reaction of carbon disulfide and excess aqueous hydrazine has been developed in which a yield of about 60% is obtained. The procedure requires the use of approximately a 5:1 mole ratio of hydrazine:carbon disulfide. For the quantities of starting materials employed (0.2 mole CS_2) in this investigation, it was found that a reflux time of from $\frac{1}{2}$ to $1\frac{1}{2}$ hours is desirable. Acidification of the reaction mixture results in the decomposition of hydrazinium dithiocarbazinate which is formed by the initial combination of hydrazine and carbon disulfide. The use of dilute aqueous solutions results in a reduction of the yield of thiocarbohydrazide. The employment of an alcoholic solvent offers no advantage over the use of an aqueous solution. Additional quantities of thiocarbohydrazide (as much as 15%) are obtained by refluxing the mother liquor, subsequent to removal of the product from the initial reaction mixture. If the reaction is carried out on a larger scale (using molar quantities of CS_2 rather than 0.2 mole), an increase in the yield of several percent is obtained.

This new procedure possesses several advantages over previously reported methods: 1) better overall yields (60%) are obtained, 2) commercially available raw materials are employed (other methods require the preparation of special starting materials) and 3) the starting materials are not as difficult to handle as in the preparation of thiocarbohydrazide by the hydrazinolysis of thiophosgene (1) (4).

The new procedure is believed to be adaptable to a semi-continuous and/or continuous operation.

A mechanism for the elimination of hydrogen sulfide from hydrazinium dithiocarbazinate to give thiocarbohydrazide has been proposed. This mechanism involves the formation of an intermediate dithiocarbazinate ion which could then react with hydrazine prior to the elimination of hydrogen sulfide. Credence is lent to this mechanism as the excess hydrazine, which is required to give good yields of thiocarbohydrazide, favors each step of the postulated mechanism.

II. ADDITION OF CYANAMIDE TO HYDRAZIDES

HISTORICAL

The addition of cyanamide to hydrazides (equation 1) is similar to the condensations of cyanate and thiocyanate with hydrazides. Certain analogies exist, namely, first, the reagents attach themselves to the β -nitrogen atom of the hydrazide group, secondly, the proposed mechanisms involve either rearrangement of an intermediate salt or molecular addition of the hydrazide across the carbon-nitrogen triple bond and thirdly, the condensations are pH dependent as a result of the stability of the reagents and/or products. It is more probable that cyanamide addition occurs according to the proposed molecular addition mechanism as the existence of a cyanamide salt in aqueous solution is improbable as a result of the weakly acidic character of cyanamide. Furthermore, cyanate and thiocyanate are relatively stable in alkaline solution as compared to cyanamide which readily undergoes polymerization to dicyandiamide under these conditions.

The procedures employed to affect cyanamide addition to hydrazides entail: 1) the use of an aqueous solution of cyanamide, 2) the employment of acidic aqueous solutions of sodium or calcium cyanamide, 3) the decomposition of nitrosoguanidine in aqueous solution and 4) the hydrazinolysis of S-alkylisothiuronium salts.

Although there are numerous reports in the literature concerning the addition of cyanamide to amines to produce guanidines, the preparation of aminoguanidine and its N-substituted derivatives represents one of the two instances of direct cyanamide condensation with hydrazine and substituted hydrazines. The preparation of bisguanylhypurazine dinitrate has also been described (5).

EXPERIMENTAL AND DISCUSSION

The addition of cyanamide to semicarbazide, thiosemicarbazide, aminoguanidine and carbohydrazide has resulted in the preparation of the expected N-guanyl derivatives. These compounds have been characterized by conversion to the corresponding picrates and/or picrolonates. The new compounds which have been prepared include:

- 1) N-carbamyl-N'-guanylhiazine hydrochloride
- 2) N-thiocarbamyl-N'-guanylhiazine hydrochloride
- 3) Bisguanylhiazine dihydrochloride
- 4) Guanylcabbohydrazide dihydrochloride

III. BIOLOGICAL ACTIVITY OF THE HYDRAZINE DERIVATIVES OF THE CARBONIC, THIOCARBONIC AND AMMONOCARBONIC ACIDS

A number of hydrazine derivatives have been evaluated for their antituberculin activity and also for their effect upon the blood pressure of hypertensive animals; however, none of the materials, which have thus far been tested, display any significant activity. The pharmacological evaluations have been carried out by personnel in the laboratories of the Eli Lilly Company.

Only a small number of hydrazine derivatives have thus far been evaluated for their insecticidal activity by the Department of Entomology at the University of Illinois. However, thiocabbohydrazide and 1-phenylthiocabbohydrazide have been found to be toxic to roaches.

A group of twenty-four hydrazine compounds consisting mainly of carbonic, thiocarbonic and ammonocarbonic acid derivatives have been subjected to an evaluation of their possible applications in the agricultural chemical field. These tests have been carried out in cooperation with the Department of Agronomy at the University of Illinois.

Results have shown that methyl hydrazine sulfate, hydrazine sulfate and thiocabbohydrazide are effective as contact herbicides. Furthermore, methyl hydrazine sulfate, hydrazine sulfate, thiosemicarbazide, thiocabbohydrazide and 1-phenylthiocabbohydrazide show promise as fungicidal or fungistatic agents. A significant effect upon the growth of certain plants has been exhibited by thiocabbohydrazide, thiosemicarbazide and 5-aminotetrazole. A small number of hydrazine compounds display crop plant defoliant activity. An interesting obser-

vation which has been made during these biological tests is the production of albinism by bisthiocarbamylhydrazine, 5-aminotetrazole and 1,2-diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole.

The results of these biological tests have repeatedly demonstrated that the presence of a thiohydrazide group $\text{—C(S)N}_2\text{H}_3$, enhances the biological activity of the compounds which have thus far been evaluated.

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VITA

The author was born in Denver, Colorado on May 10, 1924. He received his primary and secondary education in the schools of that city and was graduated from West Denver High School in June, 1942.

He attended the University of Texas, Austin, Texas, from September, 1942 until May, 1943 at which time he was drafted for military service.

He served thirty-two months in the Army of the United States and spent twenty-six months in the Southwest Pacific Theater of Operations. He received an Honorable Discharge of January 3, 1946 with the grade of Technical Sergeant.

He entered the University of Denver, Denver, Colorado, in June, 1946 and received the degree of Bachelor of Science in Chemistry in March, 1949. He began his graduate training at the University of Denver during which time he served as a graduate assistant in qualitative and quantitative analysis. He was awarded the degree of Master of Science in December, 1949.

He entered the Graduate College of the University of Illinois in February, 1950 as a research assistant working on a research program sponsored by the Office of Naval Research. He served as a teaching assistant from September, 1950 until June, 1951. At this time he received an A. D. Little Company research assistantship and in September, 1951 was appointed to the Western Cartridge Company Fellowship in Chemistry which he has held to date.

The author was married to Miss Annette Jane Simon on September 5, 1948. They have one son, Marc Jeffrey.

The author is a member of Phi Lambda Upsilon, Sigma Xi, and Alpha Chi Sigma.

